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<b>(54) Title:</b> HYDROXAMIC ACID DERIVATIVES AND THEIR USE AS ANTI-INFLAMMATORY COMPOUNDS  <b>(57) Abstract</b>  The present invention is concerned with novel hydroxamic acid derivatives of formula (I) and their use in medical therapy, particularly in the treatment of a clinical condition for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachadonic acid metabolic pathway is indicated. The invention also relates to pharmaceutical formulations and processes for the preparation of compounds according to the invention.		

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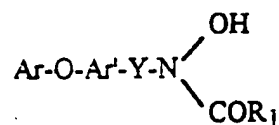
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## HYDROXAMIC ACID DERIVATIVES AND THEIR USE AS ANTI-INFLAMMATORY COMPOUNDS

The present invention is concerned with novel hydroxamic acid derivatives having anti-inflammatory activity, with processes for their preparation, with pharmaceutical formulations containing said derivatives and with their use in medicine.

European Patent Specification 0196184 describes hydroxamic acid derivatives having anti-inflammatory activity by virtue of their ability to inhibit the enzymes 5-lipoxygenase and cyclooxygenase in the mammalian arachidonic acid cascade. The compounds in question include those of formula



wherein:

Ar is phenyl;

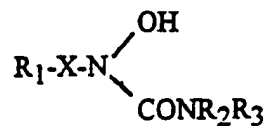
Ar' is phenylene;

Y is C<sub>2-10</sub> alkenylene;

R<sub>1</sub> is C<sub>1-4</sub> alkyl, amino, C<sub>1-4</sub> alkylamino, or di-C<sub>1-4</sub> alkylamino;

and Ar and Ar' are optionally substituted by one or more substituents independently selected from C<sub>1-4</sub> alkyl (which may itself be optionally substituted by one or more halogen atoms), C<sub>1-4</sub> alkoxy, halo, nitro, amino, carboxy, C<sub>1-4</sub> alkoxy carbonyl and hydroxy.

International patent application WO 90/12008 describes urea based lipoxygenase inhibiting compounds including those of formula



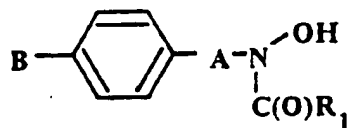
wherein:

R<sub>1</sub> is phenyl substituted by carbocyclic aryloxy optionally substituted by one, two, or three groups independently selected from halo, nitro, cyano, alkyl, alkoxy, and halosubstituted alkyl;

X is C<sub>2-6</sub> alkenylene; and

R<sub>2</sub> and R<sub>3</sub> are independently selected from hydrogen, C<sub>1-6</sub> alkyl, and carbocyclic aryl.

International patent application WO92/10469 describes hydroxamic acid derivatives, including those of formula



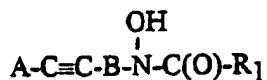
wherein:

B is aryl or aryl substituted with one or more substituents selected from a group including halo, cyano, aminocarbonyl, C<sub>1-6</sub> alkylaminocarbonyl, di C<sub>1-6</sub> alkylaminocarbonyl, and C<sub>1-6</sub> alkylsulphonyl;

A is alkynylene; and

R<sub>1</sub> is hydrogen, C<sub>1-4</sub> alkyl, or -NR<sub>2</sub>R<sub>3</sub> (wherein R<sub>2</sub> and R<sub>3</sub> are independently selected from hydrogen and C<sub>1-4</sub> alkyl).

International patent application WO92/01682 describes acetylene derivatives, including those of formula



wherein:

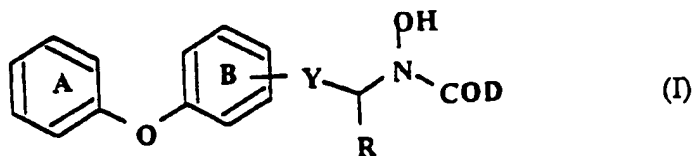
A is phenyl optionally substituted by phenoxy (optionally substituted by C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, hydroxy or halogen);

B is a bond or a straight or branched divalent C<sub>1-12</sub> alkylene group; and

R<sub>1</sub> is hydrogen, C<sub>1-12</sub> alkyl, C<sub>3-8</sub> cycloalkyl, or -NR<sub>2</sub>R<sub>3</sub> (wherein R<sub>2</sub> and R<sub>3</sub> are independently selected from hydrogen and C<sub>1-6</sub> alkyl).

A group of compounds, related to those described in EP 0196184, WO 92/10469, WO 92/01682, and WO 90/12008 has now been discovered which have use in the prophylaxis and treatment of clinical conditions for which an inhibitor of the lipoxigenase or cyclooxygenase mediated arachadonic acid metabolic pathway is indicated.

Therefore, according to the present invention, there is provided a group of compounds of formula (I)



wherein:

One/both of rings A and B is/are substituted by one or more groups independently selected from halo, cyano, -CONR<sup>1</sup>R<sup>2</sup> (wherein R<sup>1</sup> and R<sup>2</sup> are independently selected from hydrogen and C<sub>1-4</sub> alkyl), and -S(O)<sub>n</sub>R<sup>3</sup> (wherein n is an integer of from 0 to 2, and R<sup>3</sup> is C<sub>1-4</sub> alkyl, C<sub>6-10</sub> aryl, or C<sub>8-12</sub> aralkyl);

Y is -HC=CH- ((E) or (Z)), or -C≡C-;

D is C<sub>1-4</sub> alkyl or -NR<sup>4</sup>R<sup>5</sup> (wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from hydrogen and C<sub>1-4</sub> alkyl); and

R is hydrogen or C<sub>1-4</sub> alkyl;

with the proviso that (i) at least one of the substituents on rings A and/or B is other than halo; and (ii) the compound of formula (I) is not N-hydroxy-N-(1-methyl-3-{3-[4-(methylthio)phenoxy]phenyl}-2-propynyl)-urea;

or a salt, solvate or physiologically functional derivative thereof.

It will be appreciated that some compounds of formula (I) and their salts may exist in (R) or (S) enantiomeric forms. The present invention therefore includes within its scope each of the individual (R) and (S) enantiomers of the compounds of formula (I) and their salts substantially free, ie associated with less than 5%, of the other enantiomer and mixtures of such enantiomers in any proportions including racemic mixtures containing substantially equal amounts of the two enantiomers.

By the term halo is meant fluoro, chloro, bromo, or iodo; most preferably fluoro.

Ring A may be unsubstituted or substituted by 1 to 5 groups independently selected from those listed in the definition of formula (I); preferably, ring A is unsubstituted or is substituted by one group selected from halo, cyano, and  $-\text{SO}_2\text{CH}_3$ .

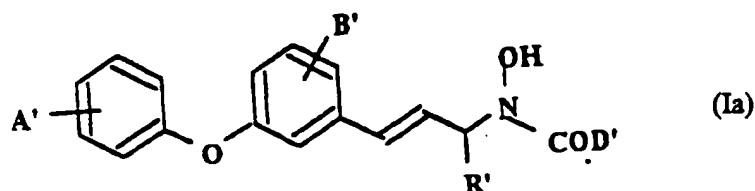
Ring B may be unsubstituted or substituted by 1 to 4 groups independently selected from those listed in the definition of formula (I); preferably, ring B is unsubstituted or is substituted by a cyano group.

Group Y may be attached to ring B at the 2-, 3-, or 4- position; preferably, the 3-position; relative to the -O- bridging group.

R is preferably methyl.

D is preferably methyl or amino; most preferably methyl.

According to a further aspect, the present invention provides compounds of formula (Ia)



wherein:

A' and B' are independently selected from hydrogen, halo, cyano,  $-\text{CONR}^{1a}\text{R}^{2a}$  (where  $\text{R}^{1a}$  and  $\text{R}^{2a}$  are independently selected from hydrogen and  $\text{C}_{1-4}$  alkyl), and  $-\text{S}(\text{O})_m\text{R}^{3a}$  (where m is an integer of from 0 to 2 and  $\text{R}^{3a}$  is  $\text{C}_{1-4}$  alkyl,  $\text{C}_{6-10}$  aryl, or  $\text{C}_{8-12}$  aralkyl); and

D' is  $\text{C}_{1-4}$  alkyl or  $-\text{NR}^{4a}\text{R}^{5a}$  (where  $\text{R}^{4a}$  and  $\text{R}^{5a}$  are independently selected from hydrogen and  $\text{C}_{1-4}$  alkyl); and

R' is  $\text{C}_{1-4}$  alkyl;

with the proviso that at least one of A' and B' is other than hydrogen or halogen;

or a salt, solvate, or a physiologically functional derivative thereof.

In a further aspect, the present invention provides compounds of formula (I) wherein D is  $\text{C}_{1-4}$  alkyl;

or a salt, solvate, or physiologically functional derivative thereof.

In a yet a further aspect, the present invention provides compounds of formula (I) wherein Y is  $-\text{CH}=\text{CH}-$ , preferably in the (E) configuration;

or a salt, solvate, or physiologically functional derivative thereof.

In a yet a further aspect, the present invention provides compounds of formula (I) wherein Y is  $-\text{CH}\equiv\text{CH}-$ , and at least one of the substituents on ring A is other than halogen;

or a salt, solvate, or physiologically functional derivative thereof.

Preferred compounds of formula (I) include those wherein:

One/both of rings A and B is/are substituted by one group selected from halo, cyano, and  $-\text{SO}_2\text{CH}_3$ ;

Y is attached to ring B at the 3-position relative to the -O- bridging group;

R is methyl; and

D is methyl or amino;

or a salt, solvate, or physiologically functional derivative thereof.

Particularly preferred compounds of formula (I) include:

(E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[4-Cyano-3-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[2-Cyano-5-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[2-Cyano-3-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[3-(4-Cyanophenoxy)phenyl]prop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[5-(4-Cyanophenoxy)-2-cyanophenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[2-Cyano-5-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[2-Cyano-3-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[2-Cyano-3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea;



(E)-1-{3-[3-(4-Cyanophenoxy)-2-cyanophenyl]-1(R)-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[4-Cyano-3-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[3-(4-mesyloxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}acetohydroxamic acid;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}acetohydroxamic acid;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}acetohydroxamic acid;

N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}acetohydroxamic acid;

or a salt, solvate, or physiologically functional derivative thereof.

Salts of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion is pharmaceutically acceptable. However, salts having non-pharmaceutically acceptable counterions are within the ambit of the present invention, either for use in non-medical applications or as intermediates in the preparation of compounds of formula (I) and their pharmaceutically acceptable salts and physiologically functional derivatives.

Salts according to the invention include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine, and salts with amino acids, such as arginine and lysine. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids.

By the term physiologically functional derivatives is meant chemical derivatives of compounds of formula (I) which have the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include compounds of formula (I) in which the hydroxyl of the hydroxamic acid functional group has been converted to a pharmaceutically acceptable salt, a urethane or an ester.

As mentioned hereinbefore, compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof have use in the prophylaxis and treatment of clinical conditions for which an inhibitor of the lipoxxygenase or cyclooxygenase mediated arachadonic acid metabolic pathway is indicated, as demonstrated hereinafter in the 5-lipoxxygenase and cyclooxygenase inhibition assays in which representative compounds of the present invention have been shown to be active. For example, the ability of compounds of formula (I) to inhibit the lipoxxygenase and cyclooxygenase mediated arachadonic acid metabolic pathways, renders them useful for the prophylaxis and treatment of spasmogenic conditions, allergic conditions, tumour formation, conditions involving blood platelet aggregation, and inflammatory conditions.

Examples of spasmogenic conditions are those involving smooth muscle tissue, especially airway smooth muscle constriction such as asthma (including idiopathic bronchial asthma), bronchitis and arterial smooth muscle constriction such as coronary spasm (including that associated with myocardial infarction, which may or may not lead to left ventricular failure resulting in cardiac asthma), ischemia-induced myocardial injury, and cerebral spasm or 'stroke' (which may lead to central nervous pathophysiology). Other examples include bowel disease caused by abnormal colonic muscular contraction such as the conditions known as 'irritable bowel syndrome', 'spastic colon' and 'mucous colitis'.

Examples of allergic conditions are extrinsic asthma, allergic skin diseases having a total or partial allergic origin, such as eczema, allergic bowel diseases (including coeliac disease), allergic eye conditions, such as hayfever (which may additionally or alternatively affect the upper respiratory tract), allergic rhinitis, and allergic conjunctivitis.

Examples of tumours are skin neoplasms, mastocytoma and other forms of cellular proliferation, both benign and malignant. It is to be noted that the effectiveness of the present compounds in the prophylaxis and treatment of tumours may arise from properties in addition to 5-lipoxygenase inhibition which also inhibit cell proliferation.

Examples of conditions involving blood platelet aggregation are those resulting from thrombosis, including 'strokes' having a total or partial thrombotic origin, coronary thrombosis, phlebitis and phlebothrombosis (the latter two conditions also possibly being associated with inflammation).

Examples of inflammatory conditions are those of the lungs, joints, eyes, bowel, skin, and heart; particularly those associated with the infiltration of leucocytes into inflamed tissue. Inflammatory lung conditions include asthma, adult respiratory distress syndrome, bronchitis and cystic fibrosis (which may additionally or alternatively involve the bowel or other tissue(s)). Inflammatory joint conditions include rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions. Inflammatory eye conditions include uveitis (including iritis) and conjunctivitis. Inflammatory bowel conditions include Crohn's disease, ulcerative colitis and distal proctitis. Inflammatory skin diseases include those associated with cell proliferation, such as psoriasis, eczema and dermatitis (whether or not of allergic origin). Inflammatory conditions of the heart include coronary infarct damage. Other inflammatory conditions include tissue necrosis in chronic inflammation, endotoxin shock, smooth muscle proliferation disorders (for example, restenosis following angioplasty), and tissue rejection following transplant surgery.

In view of their unique properties the compounds of the invention may also be employed in the prophylaxis or treatment of bone disorders (for example, osteoporosis), bacterial and fungal infections, dysmenorrhoea, multiple sclerosis and clinical conditions for which an immunosuppressant, anti-convulsant, or analgesic is indicated. The compounds of the invention also exhibit hypocholesterolaemic activity.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachadonic acid metabolic pathway, for example, a 5-lipoxygenase or cyclooxygenase inhibitor, is indicated; which comprises administration of a therapeutically effective amount of a compound of formula (I), or a

pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The present invention further provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, which clinical condition is a spasmogenic condition, an allergic condition, tumour formation, a condition involving blood platelet aggregation, or an inflammatory condition; which comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

In the alternative, there is also provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy; particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an inhibitor of the lipoxxygenase or cyclooxygenase mediated arachadonic acid metabolic pathway, for example, a 5-lipoxxygenase or cyclooxygenase inhibitor, is indicated; for example a spasmogenic condition, an allergic condition, tumour formation, a condition involving blood platelet aggregation, or an inflammatory condition.

The amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. A suitable daily dose for a mammal suffering from, or likely to suffer from, any of the clinical conditions described hereinbefore is in the range 0.1 $\mu$ g - 500mg of compound/kilogram bodyweight. In the case of systemic administration, the daily dose is typically in the range 0.05 - 500mg of compound/kilogram bodyweight, the most preferred dosage being from 0.05 to 50mg/kg bodyweight, for example, from 0.1 to 10mg/kg, administered as two or three sub-doses daily. In the case of topical administration, e.g. to the skin or eye, a suitable dose is in the range 0.1ng - 100 $\mu$ g of base per kilogram, typically about 0.1 $\mu$ g/kg.

In the case of oral dosing for the prophylaxis or treatment of airway smooth muscle constriction, for example, in asthma or bronchitis, a suitable dose of the compound of the invention may be as specified in the preceding paragraph, but preferably is from 0.1mg to 10mg of compound/kilogram bodyweight, the most preferred dosage being

from 0.1mg to 5mg/kg bodyweight. In the case of pulmonary administration, the dose is typically in the range  $2\mu\text{g}$  - 100mg/kg, preferably, from  $5\mu\text{g}$  to 5mg/kg, for example from 0.01 to 1 mg/kg.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which an inhibitor of the lipoxxygenase or cyclooxygenase mediated arachadonic acid metabolic pathway, for example, a 5-lipoxxygenase or cyclooxygenase inhibitor, is indicated; for example a spasmogenic condition, an allergic condition, tumour formation, a condition involving blood platelet aggregation, or an inflammatory condition.

While it is possible for the compound of formula (I), or a salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation. Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The carrier or excipient must, of course, be compatible with the other ingredients in the formulation and must not be detrimental to the recipient. The active ingredient may comprise from 0.1% to 99.9% by weight of the formulation. Typical unit doses of a formulation according to the invention contain from 0.01mg to 1g of the active ingredient. For topical administration, the active ingredient preferably constitutes from 1% to 2% by weight of the formulation, but the active ingredient may constitute as much as 10% w/w. Formulations suitable for nasal or buccal administration, typically contain from 0.1 to 20% w/w, for example, 2% w/w of the active ingredient.

Formulations according to the invention include those in a form suitable for oral, pulmonary, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), intra-articular, topical, or nasal/buccal administration.

The formulations of the invention may conveniently be presented in unit dosage form and may be prepared by any method well known in the art of pharmacy. All such methods include the step of bringing the active ingredient into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier, or both, and then, if desired, shaping the product into the required form.

Formulations according to the present invention which are suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous or non-aqueous liquid; or in the form of an oil-in-water or water-in-oil emulsion. The active ingredient may also be in the form of a bolus, electuary, or paste.

A tablet may be made by compressing or moulding the active ingredient, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, and/or surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration typically comprise a sterile aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient, which latter may be in microcrystalline form, for example, an aqueous microcrystalline suspension. Liposomal formulations and biodegradable polymer systems may also be used to present the active ingredient for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration include liquid and semi-liquid preparations such as liniments, lotions and applications; oil-in-water and water-in-oil emulsions such as creams, ointments and pastes; and solutions and suspensions such as drops. For example, for ophthalmic administration, the active ingredient may be presented as aqueous eye drops, for example, in the form of a 0.1 - 1.0% w/v solution.

Suitable formulations for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers, or insufflators.

For pulmonary administration via the mouth, the particle size of the powder or droplets is typically in the range 0.5 - 10 $\mu$ m, preferably 1 - 5 $\mu$ m, to ensure delivery into the bronchial tree. For nasal administration, a particle size in the range 10 - 500 $\mu$ m is preferred to ensure retention in the nasal cavity.

Metered dose inhalers are pressurised aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquefied propellant. During use, these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150 $\mu$ l, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, anti-oxidants and suitable flavouring agents.

Nebulisers are commercially available devices that transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas through a narrow venturi orifice, typically air or oxygen, or by

means of ultrasonic agitation. Suitable formulations for use in nebulisers consist of the active ingredient in a liquid carrier and comprising up to 40% w/w of the formulation, preferably less than 20% w/w. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxy-benzoate, anti-oxidants, flavouring agents, volatile oils, buffering agents and surfactants.

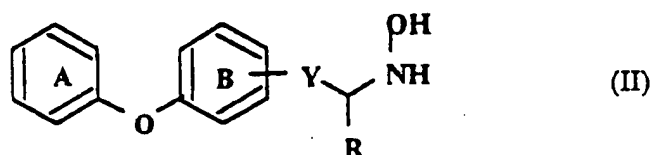
Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation.

In addition to the aforementioned ingredients, formulations according to the invention may include one or more additional ingredients such as diluents, buffers, flavouring agents, binders, compression aids, disintegrants, surface active agents, thickeners, lubricants, preservatives, for example, methyl hydroxybenzoate, anti-oxidants and emulsifying agents. The compounds of the invention may advantageously be employed in combination with one or more other therapeutic ingredients selected from an antibiotic (for example, an anti-bacterial), anti-fungal, or anti-viral agent, an anti-histamine (particularly a peripherally-acting anti-histamine), or a non-steroidal anti-inflammatory drug (NSAID).

The compounds of these combinations may be administered simultaneously, for example, in the same formulation or in separate formulations, or sequentially within a sufficiently short time interval to achieve the desired combined therapeutic effect. When the compounds are employed in the same formulation, a formulation according to the invention may contain, in addition to a compound of the invention, the further ingredient(s).



According to a further aspect of the invention, there is provided a process for preparing the compounds of formula (I), or salts, solvates, or physiologically functional derivatives thereof, which comprises reacting a compound of formula (II)



wherein Y, R, and the substituents on rings A and B are as defined for the compound of formula (I), or a salt thereof, with a suitable agent or agents to effect conversion of the N-hydrogen to an N-COD group, where D is (a)  $C_{1-4}$  alkyl, or (b)  $NR^4R^5$  (wherein  $R^4$  and  $R^5$  are as defined for formula (I));

and optionally converting the compound of the formula (I) so formed to a corresponding salt, solvate, or physiologically functional derivative thereof.

Conversion (a) is typically carried out by treating of the compound of formula (II) with an acylating agent, for example, an appropriate anhydride or activated acid, such as an acid halide, for example, acetyl chloride. This reaction is suitably effected in an inert solvent, such as a halohydrocarbon, for example, dichloromethane, at a temperature in the range  $-10^\circ\text{C}$  to  $150^\circ\text{C}$ , for example  $0-25^\circ\text{C}$ .

Conversion (b) is typically carried out by treating the compound of formula (II), or a salt thereof,

- (i) where  $R^4$  and  $R^5$  are to be hydrogen with a Group I cyanate, for example, potassium cyanate, in a non-polar solvent, such as tetrahydrofuran (THF), in the presence of acid, such as a mineral acid, for example, dilute aqueous HCl, at a temperature in the range  $-10^\circ\text{C}$  to  $150^\circ$ , for example  $0-25^\circ\text{C}$ ;
- (ii) where  $R^4$  is to be  $C_{1-4}$  alkyl and  $R^5$  is to be hydrogen, with the corresponding isocyanate  $R^4\text{NCO}$ , in a suitable solvent, such as a halohydrocarbon, for

example, dichloromethane, at a temperature in the range of  $-10^{\circ}\text{C}$  to  $150^{\circ}$ , for example  $20-100^{\circ}\text{C}$ ;

- (iii) where  $\text{R}^4$  and  $\text{R}^5$  are each to be  $\text{C}_{1-4}$  alkyl, with the corresponding carbamoyl halide, for example  $\text{R}^4\text{R}^5\text{NCOCI}$ , in an inert solvent, such as a halohydrocarbon, for example, dichloromethane, in the presence of base, such as an organic base, for example, pyridine, at a temperature in the range  $-10^{\circ}\text{C}$  to  $150^{\circ}\text{C}$ , for example,  $20-100^{\circ}\text{C}$ .

Compounds of formula (II), and salts thereof, may be prepared by acid or base hydrolysis of the corresponding N,O- or O- blocked compound, for example, the  $-\text{N}(\text{CO}_2\text{Me})\text{OCO}_2\text{Me}$ , or  $-\text{N}(\text{Boc})\text{OBoc}$  or  $-\text{N}(\text{Boc})\text{OH}$  compound where Boc is *t*-butoxycarbonyl. For example, where the  $-\text{N}(\text{Boc})\text{OBoc}$  or  $-\text{N}(\text{Boc})\text{OH}$  compound is used, the compound of formula (II), or a salt thereof, may be prepared by treatment with an acid, such as an arylsulphonic acid, for example, *p*-toluenesulphonic acid; in a non-polar solvent for example, toluene; at a moderate temperature, suitably in the range  $10^{\circ}-100^{\circ}\text{C}$ , for example,  $50-60^{\circ}\text{C}$ . The resulting salt of the compound of formula (II) may then optionally be treated to release the free base, for example, by chromatography on silica. The N,O- or O- blocked compound may be obtained by reaction of the corresponding compound of formula (III)



wherein Y and R are as defined for formula (I) and P is a protecting group, such as  $-\text{CO}_2\text{Me}$  or *t*-butoxycarbonyl, with a compound of formula (IV)



wherein rings A and B are optionally substituted as described for formula (I) and L is a suitable leaving group, for example, a halogen, (typically bromo or iodo) or trifluoromethanesulfonate; typically at elevated temperature in the presence of a

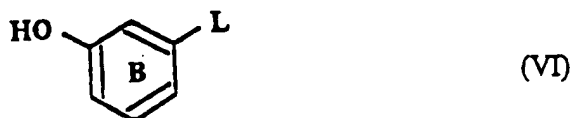
catalyst, such as palladium (II) acetate, tri(o-tolyl)phosphine, and a suitable base, for example, triethylamine.

Compounds of formula (III) may be obtained by one or more of the methods described in EP 0384594.

Compounds of formula (IV) may be obtained commercially or prepared, for example, by coupling a compound of formula (V)



wherein L' is a leaving group, such as a halogen, for example, fluorine, and ring A is substituted as defined for a compound of formula (I), or a suitably protected form thereof, with a compound of formula (VI)



wherein L is as defined above for formula (IV). This coupling may be effected by reaction in the presence of an inorganic base, for example, potassium carbonate, in an aprotic solvent, for example DMF; at an elevated temperature, for example, 50-200°C.

Alternatively, compounds of formula (II) may be prepared by oximation of the corresponding ketone, for example, using hydroxylamine in a polar solvent, such as methanol, followed by reduction of the resulting oxime, for example, using sodium cyanoborohydride/oxalic acid.

The individual enantiomers of the compound of the invention may be obtained by separation of the components of the racemic mixture, for example, by means of a chiral chromatography column or by preparing and separating suitable diastereoisomers, or by direct synthesis from the corresponding chiral compound of formula (II) by the method described above.

Optional conversion of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides compounds of formula (II) as defined above, or a salt thereof, particularly a compound selected from:

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-hydroxylamine; and

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-hydroxylamine.

For a better understanding of the invention, the following Examples are given by way of illustration.

## SYNTHETIC EXAMPLES

### Synthetic Example 1

#### Preparation of (E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea

##### (a) 4-(3-Bromophenoxy)benzonitrile

Anhydrous potassium carbonate (13.9 g) was added in one portion to a stirred solution of 4-fluorobenzonitrile (12.1g, Aldrich) and 3-bromophenol (17.3g, Aldrich) in DMF (75ml). The mixture was refluxed for 6 hours, then stirred overnight at room temperature and filtered. The filtrate was evaporated in vacuo and the remaining gum partitioned between ethyl acetate (500ml) and water (300ml). The organic phase was separated, washed with 1N aqu. NaOH, 0.5N aqu. HCl and saturated brine, dried over anhydrous sodium sulphate and evaporated in vacuo to give a tan oil. This was chromatographed (Merck 9385 silica, 9:1 hexane:ethyl acetate eluant) to give the desired product as a white solid (24.5g), mp 70-72°C.

##### (b) (E)-N-t-Butoxycarbonyl-N-{3-[3-(4-cyanophenoxy)phenyl]-1-methyl-prop-2-enyl}hydroxylamine

Triethylamine (12.7g, Aldrich) was added to a stirred solution of the product from Example 1(a) (17.2g), N,O-bis(t-butoxycarbonyl)-N-[but-3-en-2-yl]hydroxylamine (19.8g, obtained from but-3-yn-2-ol by the method described in EPS 0384594, Synthetic Examples 2 and 3) and bis(tri-*o*-tolylphosphine)palladium(II) chloride (2.5g, Aldrich) in DMF (200 ml). The mixture was heated at 100-110°C for 8 hours, then stirred overnight at room temperature, evaporated in vacuo and the residue partitioned between ethyl acetate (1000ml) and water (800ml). The organic phase was separated and washed with 0.5N aqu. HCl and saturated brine, dried over anhydrous sodium sulphate and evaporated in vacuo to give an orange gum. This was chromatographed (Merck 9385 silica, 9:1 → 7:3 hexane:ethyl acetate graded eluant) to give the desired product (16.5g).

- (c) (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate

p-Toluenesulphonic acid monohydrate (9.1g, Aldrich) was added in one portion to a stirred solution of the product from Example 1(b) (16.5g) in toluene (100ml). The mixture was heated at 50-60°C for 2 hours, then stirred overnight at room temperature and the desired product (11.0g) filtered off.

- (d) (E)-1-{3-[3-(4-Cyanophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea

Potassium cyanate (14.4g, Aldrich) was added in one portion to a stirred solution of the product from Example 1(c) (26.8g) in THF (200ml)/water (10ml) at 0°C followed by the dropwise addition of 1N aqu. HCl (118ml) over 30 minutes. The mixture was stirred at room temperature for 2 hours, then poured into a mixture of ethyl acetate (1000ml) and water (500ml). The organic phase was separated and washed with 0.5N aqu. HCl, water, saturated aqu. sodium bicarbonate and saturated brine, dried over anhydrous sodium sulphate and evaporated in vacuo to give a pale tan foam. This was chromatographed on silica, using 5% to 10% methanol/dichloromethane graded eluant and the resulting solid (17.4g) recrystallised from ethyl acetate/hexane to give the desired product as a white solid (12.3g), m.p. 138-140°C.

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>) δ: 1.35 (3H, d, -CHCH<sub>3</sub>), 4.85 (1H, m, -CHCH<sub>3</sub>), 6.32 (2H, s, -NH<sub>2</sub>), 6.35 (1H, dd, -CH-), 6.50 (1H, d, -CH-), 7.0-7.85 (8H, m, aromatics), 9.02 (1H, s, -OH)

FAB MS: m/e 324 (MH<sup>+</sup>)

Microanalysis: C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub> found (calculated) %  
C 66.56 (66.86), H 5.35 (5.30), N 12.78 (13.00)

## Synthetic Example 2

### Preparation of (E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}-1-hydroxyurea

#### (a) (E)-N-t-Butoxycarbonyl-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methyl-prop-2-enyl}hydroxylamine

To a solution of the product from Example 1(a) (1.0g) in DMF (10ml) was added N,O-bis (t-butoxycarbonyl)-N-[but-3-en-2(R)-yl]hydroxylamine (1.06g, obtained from but-3-yn-2(S)-ol by the method described in EP 0384594), followed by triethylamine (0.822g), and bis(tri-*o*-tolylphosphine)palladium(II) chloride (140mg). The reaction was heated at 100-110°C for 2 hours, then stirred at room temperature overnight, and then heated for a further 3-4 hours at 100-110°C. On cooling, ethyl acetate was added and the mixture was filtered through Hyflo (Trademark). The filtrate was washed twice with 10% citric acid, twice with brine, and then dried on anhydrous sodium sulphate, filtered, and the solvent was removed *in vacuo*. Purification of the residue by flash chromatography on silica, eluting with ethyl acetate/hexane (20:80) afforded the title product.

#### (b) (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate

p-Toluenesulphonic acid monohydrate (260mg) was added to a solution of the product from Example 2(a) in toluene (8ml). The mixture was heated at 50°C for 2-3 hours, then stirred at room temperature for 24 hours. The reaction was then dried *in vacuo*, the residue taken up in toluene and the title product was precipitated by addition of diethyl ether and collected.

#### (c) (E)-1-{3-[3-(4-Cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}-1-hydroxyurea

Potassium cyanate (357mg) was added to a stirred solution of the product from Example 2(b) in THF (20ml), with cooling in an ice bath. 1N aqueous HCl (2eq) was then added dropwise, and the reaction was stirred for 1-2 hours until

reaction was complete. The organic phase was separated and then washed successively with 1N HCl, saturated sodium bicarbonate, then brine, before being dried over anhydrous sodium sulphate, filtered, and the solvent was removed in vacuo. Purification of the residue by flash chromatography on silica, eluting with methanol/dichloromethane (3:97) afforded the title product as a white solid, mp 62-64°C.

Microanalysis:  $C_{18}H_{17}N_3O_3 \cdot 0.25 H_2O$   
C 65.92 (65.94), H 5.33 (5.38), N 12.64 (12.81)

Optical Rotation ( $c=1$ , methanol, 22°) :  $[\alpha]_{Hg} = +46.14$ ,  $[\alpha]_{Na} = +30.76$

### Synthetic Example 3

#### Preparation of (E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-1-hydroxyurea

(a) (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate

The title product was obtained from 4-(3-bromophenoxy)benzonitrile and N,O-bis (t-butoxycarbonyl)-N-[but-3-en-2(S)-yl]hydroxylamine (obtained from but-3-yn-2(R)-ol by the method described in EP 0384594), by the method of Examples 1 and 2.

(b) (E)-1-{3-[3-(4-Cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-1-hydroxyurea

The title product was obtained by reaction of the product from Example 3(a) with potassium cyanate under the conditions described in Example 2(c). The product was isolated as a white solid, mp 58-60°C.

Microanalysis:  $C_{18}H_{17}N_3O_3 \cdot 0.22 H_2O$   
C 66.35 (66.05), H 5.63 (5.37), N 12.54 (12.84)

Optical Rotation ( $c=1$ , methanol, 22°) :  $[\alpha]_{Hg} = -48.06$ ,  $[\alpha]_{Na} = -32.21$



Synthetic Examples 4 - 14

The following compounds of formula (I) were prepared in a manner analogous to the method of Synthetic Examples 1 - 3. The NMR, FAB, Mass Spec., and microanalysis of each compound were consistent with the proposed structure.

- 4) (E)-1-{3-[4-Cyano-3-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea, mp 155-156°C;
- 5) (E)-1-{3-[2-Cyano-5-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea, mp 141-142°C;
- 6) (E)-1-{3-[2-Cyano-3-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea, 0.4 hydrate, mp 140-141°C;
- 7) (E)-1-{3-[3-(4-Cyanophenoxy)phenyl]prop-2-enyl}-1-hydroxyurea,  
Microanalysis:  $C_{17}H_{15}N_3O_3$   
C 65.94 (66.01), H 4.96 (4.89), N 13.30 (13.58);
- 8) (E)-1-{3-[5-(4-Cyanophenoxy)-2-cyanophenyl]-1-methylprop-2-enyl}-1-hydroxyurea,  
Microanalysis:  $C_{19}H_{16}N_4O_3$  .05  $C_4H_8O_2$   
C 64.06 (64.27), H 4.67 (5.13), N 14.50 (14.27);
- 9) (E)-1-{3-[2-Cyano-5-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea,  
Microanalysis:  $C_{18}H_{16}FN_3O_3$  .033  $H_2O$   
C 62.17 (62.25), H 4.35 (4.83), N 11.61 (12.09);
- 10) (E)-1-{3-[2-Cyano-3-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea, 0.22 hydrate, mp 160-162°C;
- 11) (E)-1-{3-[2-Cyano-3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea;  
Microanalysis:  $C_{19}H_{16}N_4O_3$  .05  $H_2O$   
C 63.84 (63.87), H 4.76 (4.76), N 15.28 (15.69);

- 12) (E)-1-{3-(4-Cyanophenoxy)-2-cyanophenyl}-1(R)-methylprop-2-enyl}-1-hydroxyurea, 0.40 hydrate, mp 174-175°C;
- 13) (E)-1-{3-[4-Cyano-3-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea, mp 151-153°C;
- 14) 85%(E)-1-{3-[3-(4-mesyphenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea  
15% 1-{3-[3-(4-mesyphenoxyl)-1-methylpropyl]-1-hydroxyurea,  
Microanalysis: 15% C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>S, 85% C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>S, 0.4CH<sub>3</sub>OH  
C 56.71 (56.78), H 5.48 (5.59), N 7.19 (7.19);

#### Synthetic Example 15

#### Preparation of (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-acetohydroxamic acid

- (a) (E)-N-t-Butoxycarbonyl-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methyl-prop-2-enyl}hydroxylamine and (E)-N,O-bis(t-Butoxycarbonyl-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methyl-prop-2-enyl}hydroxylamine

The title products were prepared by reaction of the product from Example 1(a) and N,O-bis(t-butoxycarbonyl)-N-[but-3-en-2(S)-yl]hydroxylamine (see Example 3(a)) by the method of Example 2(a). The products were purified by column chromatography on silica, eluting with ethyl acetate/hexane (1:9).

- (b) (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}hydroxylamine

The products from Example 15(a) were deprotected by heating in dry toluene with p-toluenesulphonic acid (1.05eq), under N<sub>2</sub>, at 50°C for 2 hours, and then stirring at room temperature overnight. The crude products were combined, and the solvent removed in vacuo. The residue was purified by flash chromatography on silica, eluting with methanol/dichloromethane (2:98) to afford the title product.

(c) O-Acetyl-(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methyl-prop-2-enyl} acetohydroxamic acid

To a stirred solution of the product from Example 15(b) (0.84g) in dichloromethane (20ml), was added pyridine (2eq), under N<sub>2</sub> and with cooling in an ice-bath. Acetyl chloride (2eq, Aldrich), in dichloromethane (10ml) was then added dropwise and the reaction was stirred at room temperature overnight. The resulting mixture was dried in vacuo, and the residue was partitioned between ethyl acetate and 1N HCl. The organic phase was separated, washed successively with water, saturated sodium bicarbonate (x2), water, then brine; dried over sodium sulphate, filtered and then the solvent was removed in vacuo. Purification of the residue by flash chromatography on silica, eluting with ethyl acetate/hexane (1:1) gave the title product.

(d) E-N-{3-[3-(4-Cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl} acetohydroxamic acid

To a stirred solution of the product from Example 15(c) (0.56g) in methanol (10ml), was added anhydrous potassium carbonate (0.424g) under N<sub>2</sub>, with cooling in an ice-bath. The reaction was stirred for 1-1½ hours until complete, then the solvent was removed in vacuo. The residue was partitioned between diethyl ether and 1M HCl. The organic phase was separated, washed successively with saturated sodium bicarbonate, water, and brine, then dried over sodium sulphate, filtered and dried in vacuo. Purification of the residue by flash chromatography on silica, eluting with ethyl acetate, afforded the title product as a white solid.

Microanalysis: C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> · 0.36 H<sub>2</sub>O  
C 69.27 (69.39), H 5.52 (5.74), N 8.30 (8.51)

Optical Rotation (c=1, methanol, 22°) : [α]<sub>Hg</sub> = -148.95, [α]<sub>Na</sub> = -117.20

### Synthetic Example 16

Preparation of (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl} acetohydroxamic acid, sodium salt; and (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl} acetohydroxamic acid, calcium salt;

- (a) (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl} acetohydroxamic acid, sodium salt

To a solution of the product from Example 15 (204mg) in methanol (30ml), was added sodium hydride (25.32mg) in methanol (6ml), under nitrogen. The reaction was stirred at room temperature then dried in vacuo to form the title compound.

- (b) (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl} acetohydroxamic acid, calcium salt

To a solution of the product from Example 16(a) in water, was added calcium chloride dihydrate (93mg) in water and the reaction was stirred at room temperature until the crude product precipitated. The precipitate was collected by filtration then washed with water, then diethyl ether. The product was dried at 40°C under high vacuum, mp 135°C (shrinks 100°C).

$^1\text{H}$  NMR ( $d_6$ -DMSO, 353K)  $\delta$ : 7.8 (d, 2H, Ar-H), 7.5-6.9 (m, 6H, ArH), 6.5 (s, 2H, -CH=CH-), 4.7 (br.s, 1H, CH), 2.0 (s, 3H, C(O)CH<sub>3</sub>), 1.3 (d, 3H, CH<sub>3</sub>).

Microanalysis: (C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>)<sub>2</sub> . Ca . 1.6 H<sub>2</sub>O  
C 64.19 (64.14), H 4.99 (5.04), N 7.82 (7.87).

### Synthetic Example 17

Preparation of (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl} acetohydroxamic acid

- (a) (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}  
acetohydroxamic acid, acetate ester

The title product was obtained from the product of Example 1(a) and N,O-bis(t-butoxycarbonyl)-N-[but-3-en-2(R)-yl]hydroxylamine according to the method of Example 15.

- (b) (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}  
acetohydroxamic acid

The title product was obtained from the product of Example 17(a) according to the method of Example 15(b).

Microanalysis:  $C_{19}H_{18}N_2O_3 \cdot 0.40 H_2O$   
C 69.55 (69.24), H 5.84 (5.75), N 8.52 (8.50)

Optical Rotation ( $c=1$ , methanol,  $22^\circ$ ) :  $[\alpha]_{Hg} = +117.67$ ,  $[\alpha]_{Na} = +142.04$

#### Synthetic Example 18

Preparation of (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}  
acetohydroxamic acid

The title compound was prepared from the product of Example 1(a) and N,O-bis(t-butoxycarbonyl)-N-[but-3-en-2-yl]hydroxylamine by the method of Example 15.

Microanalysis:  $C_{19}H_{18}N_2O_3$   
C 70.83 (70.79), H 5.67 (5.63), N 8.54 (8.69)

#### Synthetic Example 19

Preparation of N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}  
acetohydroxamic acid

- (a) 4-(3-Iodophenoxy)benzonitrile  
4-Fluorobenzonitrile (5.0g, Aldrich), 3-iodophenol (9.09g, Aldrich) and potassium carbonate (5.78g) were dissolved in DMF (35ml) and heated at 150° C for 3 hours. The reaction was then poured into water (100ml) and extracted three times with ethyl acetate. The combined organic extracts were washed successively with 1M sodium hydroxide, water (x2), and brine before being dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed in vacuo. The title product was obtained by recrystallising the residue from hexane.
- (b) N,O-bis(t-butoxycarbonyl)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-vnyl}hydroxylamine

To a mixture of the product from Example 19(a) (3.21g), N,O-bis (t-butoxycarbonyl)-N-[but-3-yn-2(S)-yl]hydroxylamine (2.85g) (prepared as described in Example 3 of EP 0384594) and copper (I) iodide (38mg) in triethylamine (40ml) was added bis(triphenylphosphinyl)palladium dichloride (140mg) with the exclusion of moisture. The reaction was stirred at room temperature for 2½ hours, then diluted with ethyl acetate and water. The organic phase was separated, washed successively twice with 5% citric acid, water, and brine, then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed in vacuo. Purification of the residue by flash chromatography on silica, eluting with ethyl acetate/hexane (12.5:87.5) afforded the title product.

- (c) N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-vnyl}hydroxylamine

To a solution of the product from Example 19(b) (4.5g) in toluene (50ml), was added p-toluenesulphonic acid (1.90g). The reaction was heated at 50-60°C for 2 hours under N<sub>2</sub> then stirred at room temperature until reaction was complete. The mixture was then diluted with diethyl ether, filtered, and the precipitate washed with diethyl ether to give the p-toluenesulphonate salt of the title compound.

The p-toluenesulphonate salt (2.2g) was stirred with a solution of potassium carbonate (2g) in water (50ml), then extracted 3 times with ethyl acetate. The combined organic phases were washed with water, then semi-saturated brine,

before being dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed in vacuo.

(d) O-Acetyl-N-1-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-ynyl}acetohydroxamic acid

To a stirred solution of the product from Example 19(c) (1.35g) in dichloromethane (25ml), was added pyridine (0.77g) followed by acetyl chloride (0.77g) in dichloromethane (10ml), cooling with an ice-bath under  $\text{N}_2$ . The reaction was stirred at room temperature overnight under  $\text{N}_2$  before removing the solvent in vacuo. The residue was partitioned between ethyl acetate and 1M HCl and the separated organic layer was washed with 1M HCl, twice with  $\text{NaHCO}_3$ , then with brine, before being dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed in vacuo. Purification of the residue by flash chromatography using ethyl acetate/hexane (1:1) afforded the title compound.

(e) N-1-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-ynyl}acetohydroxamic acid

To a stirred solution of the product from Example 19(d) (1.39g) in methanol (20ml) was added potassium carbonate (1.06g), cooling with an ice-bath under  $\text{N}_2$ . The reaction was stirred at room temperature for 1-2 hours, then the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and 1M HCl. The separated organic phase was washed with water, saturated  $\text{NaHCO}_3$ , water, then with brine, before being dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed in vacuo. Purification of the residue by flash chromatography on silica, eluting with ethyl acetate, afforded the title product.

$^1\text{H}$  NMR ( $\text{d}_6$  DMSO)  $\delta$ : 9.8 (s, 1H, N-OH), 7.9-7.1 (m, 8H, ArH), 5.5 (q, 1H, CH), 2.0 (s, 3H,  $\text{C}(\text{O})\text{CH}_3$ ), 1.4 (d, 3H,  $\text{CH}_3$ ).

Microanalysis:  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$   
C 70.97 (71.24), H 5.29 (5.03), N 8.46 (8.74)

### PHARMACEUTICAL FORMULATION EXAMPLES

The "active ingredient" in the following formulations is as defined above; preferably one of the compounds of Synthetic Examples 1 to 18.

#### Example A: Oral Tablet (i)

	<u>Per tablet</u>
Active Ingredient	50.0 mg
Lactose	61.0 mg
Sodium Starch Glycollate	10.0 mg
Povidone	3.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient, lactose and starch. Granulate the powders using a solution of povidone in purified water. Dry the granules, add the magnesium stearate and compress to produce tablets.

#### Example B: Ointment

Active Ingredient	1.0 g
White Soft Paraffin	to 100.0 g

Disperse the active ingredient in a small volume of the vehicle. Gradually incorporate this into the bulk to produce a smooth, homogeneous product. Fill into collapsible metal tubes.

#### Example C: Cream for topical use

Active Ingredient	1.0 g
Polawax GP 200	20.0 g
Lanolin Anhydrous	2.0 g
White Beeswax	2.5 g
Methyl hydroxybenzoate	0.1 g
Distilled Water	to 100.0 g



Heat the Polawax, beeswax and lanolin together at 60°C. Add a solution of methyl hydroxybenzoate. Homogenise using high speed stirring. Allow the temperature to fall to 50°C. Add and disperse the active ingredient. Allow to cool with slow speed stirring.

Example D: Lotion for topical use

Active Ingredient	1.0 g
Sorbitan Monolaurate	0.6 g
Polysorbate 20	0.6 g
Cetostearyl Alcohol	1.2 g
Glycerin	6.0 g
Methyl Hydroxybenzoate	0.2 g
Purified Water B.P.	to 100 ml

The methyl hydroxybenzoate and glycerin were dissolved in 70ml of the water at 75°C. The sorbitan monolaurate, Polysorbate 20 and cetostearyl alcohol were melted together at 75°C and added to the aqueous solution. The resulting emulsion was homogenised, allowed to cool with continuous stirring and the active ingredient added as a suspension in the remaining water. The whole was stirred until homogeneous.

Example E: Oral Tablet (ii)

	<u>Per tablet</u>
Active Ingredient	10.0 mg
Lactose	80.0 mg
Microcrystalline Cellulose	40.0 mg
Povidone	4.0 mg
Sodium Starch Glycollate	15.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient and microcrystalline cullolose before blending with lactose, povidone and sodium starch glycollate. Lubricate with magnesium stearate and compress to produce tablets (150mg per tablet).

Example F: Oral capsule

Active Ingredient	25.0 mg
Starch 1500	100.0 mg
Sodium Starch Glycollate	14.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient, Starch 1500 and sodium starch glycollate before blending with magnesium stearate. Fill power into Size 3 capsule shells (140 mg per capsule).

Example G: Powder capsules for inhalation

Active Ingredient (0.5-7.0 $\mu$ m powder)	1.0 mg
Lactose (30-90 $\mu$ m powder)	49.0 mg

The powders were mixed until homogeneous and filled into suitably sized hard gelatin capsules (50mg per capsule).

Example H: Inhalation aerosol

Active Ingredient (0.5-7.0 $\mu$ m powder)	50.0 mg
Sorbitan Trioleate	100.0 mg
Saccharin Sodium (0.5-7.0 $\mu$ m powder)	5.0 mg
Methanol	2.0 mg
Trichlorofluoromethane	4.2 g
Dichlorodifluoromethane	to 10.0 ml

The sorbitan trioleate and menthol were dissolved in the trichloro-fluoromethane. The saccharin sodium and active ingredient were dispersed in the mixture which was then transferred to a suitable aerosol canister and the dichlorofluoromethane injected through the valve system. This composition provides 0.5mg of active ingredient in each 100 $\mu$ l dose.

## BIOLOGICAL DATA

### Ex vivo inhibition of 5-lipoxygenase

Preliminary studies in rabbits indicated that the compound of the Synthetic Examples effectively inhibited the stimulated synthesis of leukotriene B<sub>4</sub> (LTB<sub>4</sub>), a compound formed from arachidonic acid via the 5-lipoxygenase pathway.

The test compound was administered both intravenously. (1/4 DMSO/3/4 PEG 200) and orally. (0.25% celacol). The concentration of LTB<sub>4</sub> in the plasma was measured periodically and expressed as a percentage of the mean control value. The procedure used is described in Br. J. Pharmacol. 94, 528 (1988) and may be summarised as follows.

Within 2 minutes of collection, duplicate samples (0.5ml) of blood were equilibrated at 37°C for 5 minutes and then stimulated with the calcium ionophore A23187 (10μl, final concentration 15μg/ml) for a further 30 minutes at 37°C. When incubation was complete, the samples were centrifuged (10,000rpm for 2 minutes at 0°C) and the cell-free plasma removed. The plasma concentration of LTB<sub>4</sub> was determined by specific radioimmunoassay.

At 2mg/kg oral dosing, the compounds of Synthetic Examples 1 and 15 inhibited ex vivo LTB<sub>4</sub> production by more than 80% for over 12 hours. Under the same conditions, the compounds of Synthetic Examples 2, 3, 11, and 18 gave 80% inhibition for at least one hour. Compounds of the other Synthetic Examples were either untested or gave less than 80% inhibition.

### In vitro inhibition of 5-lipoxygenase

Leukocytes were isolated from blood donated by normal aspirin-free volunteers by washing and centrifugation. A solution of the test compound in DMSO (10μl, final concentration 0.01 - 100μM) was added to the washed cell suspension (480μl) and the mixture incubated at room temperature for 5 minutes. The tubes were placed on ice for 5 minutes and then stimulated with the calcium ionophore A23157 (10μl, final concentration 2.0μM) for 5 minutes at 37°C. The reaction was terminated by boiling

and the plasma concentration of LTB<sub>4</sub> determined by Scintillation Proximity Assay (SPA).

Each of the compounds of Synthetic Examples 1-19, when tested in this screen, was found to have an average IC<sub>50</sub> of less than 1μM, with the exception of Synthetic Examples 8 (2.49μM), 12 (2.79μM), and 14 (1.48μM).

#### In Vitro inhibition of cyclooxygenase

Washed platelet suspensions from healthy human donors were prepared according to the method of Radomski *et al* (Thromb. Res., 30, 383-393, 1983). Tubes containing aliquots (0.5ml) of platelet suspension (10<sup>7</sup> cells/ml) were incubated with test drug or vehicle for 5 minutes at room temperature before being placed on an ice bath for a further 5 minutes. The calcium ionophore A-23187 was added (final concentration 2μM) and the tubes were incubated for 5 minutes at 37°C. The reaction was terminated by boiling for 2 minutes and the cellular precipitate removed for centrifugation. The thromboxane B<sub>2</sub> content of the supernatant was determined by radio-immunoassay.

The compounds of Synthetic Examples 6, 10, 15, and 19, when tested in this screen, were found to have an IC<sub>50</sub> of less than 10μM.

#### Bronchoconstriction Assay in the Guinea Pig

The animals were pre-sensitised to antigen (ovalbumin) 2 to 3 weeks prior to testing in the bronchospasm model. Compounds were given to the animals orally, 1-6 hours before antigen challenge at a dose of 10mg/kg. Control animals were dosed only with vehicle. The time of dosing before challenge was noted. Indomethacin and mepyramine were also given 10 minutes before challenge.

A measured challenge of nebulised antigen was given to anaesthetised animals to promote an allergic asthma-like response, and the change in pulmonary inflation pressure (PIP) measured. PIP was measured continuously from before the challenge for 11 minutes.

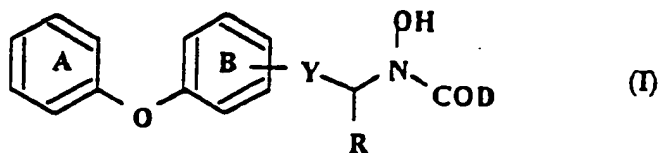
The compound of Synthetic Example 1, when given 1 hour before challenge gave 64% inhibition of response. The compound of Synthetic Example 15 gave 66% inhibition of response when given 6 hours before challenge.

#### Toxicity

The compounds of Synthetic Examples 1, 11, and 15 were tested in female Wistar rats at 10, 100, and 500 mg/kg/day over 14 days. No serious toxic effects were observed.

Claims

## 1. Compounds of formula (I)



wherein:

One/both of rings A and B is/are substituted by one or more groups independently selected from halo, cyano,  $-\text{CONR}^1\text{R}^2$  (wherein  $\text{R}^1$  and  $\text{R}^2$  are independently selected from hydrogen and  $\text{C}_{1-4}$  alkyl), and  $-\text{S}(\text{O})_n\text{R}^3$  (wherein  $n$  is an integer of from 0 to 2, and  $\text{R}^3$  is  $\text{C}_{1-4}$  alkyl,  $\text{C}_{6-10}$  aryl, or  $\text{C}_{8-12}$  aralkyl);

Y is  $-\text{HC}=\text{CH}-$  ((E) or (Z)), or  $-\text{C}\equiv\text{C}-$ ;

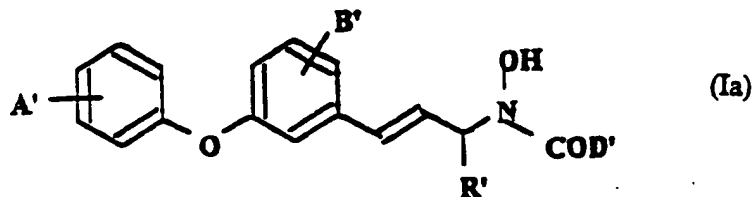
D is  $\text{C}_{1-4}$  alkyl or  $-\text{NR}^4\text{R}^5$  (wherein  $\text{R}^4$  and  $\text{R}^5$  are independently selected from hydrogen and  $\text{C}_{1-4}$  alkyl); and

R is hydrogen or  $\text{C}_{1-4}$  alkyl;

with the proviso that (i) at least one of the substituents on rings A and/or B is other than halo; and (ii) the compound of formula (I) is not N-hydroxy-N-(1-methyl-3-{3-[4-(methylthio)phenoxy]phenyl}-2-propynyl)-urea;

or a salt, solvate or physiologically functional derivative thereof.

## 2. Compounds of formula (Ia)



wherein:

A' and B' are independently selected from hydrogen, halo, cyano, -CONR<sup>1a</sup>R<sup>2a</sup> (where R<sup>1a</sup> and R<sup>2a</sup> are independently selected from hydrogen and C<sub>1-4</sub> alkyl), and -S(O)<sub>m</sub>R<sup>3a</sup> (where m is an integer of from 0 to 2 and R<sup>3a</sup> is C<sub>1-4</sub> alkyl, C<sub>6-10</sub> aryl, or C<sub>8-12</sub> aralkyl); and

D' is C<sub>1-4</sub> alkyl or -NR<sup>4a</sup>R<sup>5a</sup> (where R<sup>4a</sup> and R<sup>5a</sup> are independently selected from hydrogen and C<sub>1-4</sub> alkyl); and

R' is C<sub>1-4</sub> alkyl;

with the proviso that at least one of A' and B' is other than hydrogen or halogen;

or a salt, solvate, or a physiologically functional derivative thereof.

3. Compounds of formula (I) according to claim 1

wherein:

One/both of rings A and B is/are substituted by one group selected from halo, cyano, and -SO<sub>2</sub>CH<sub>3</sub>;

Y is attached to ring B at the 3-position relative to the -O- bridging group;

R is methyl; and

D is methyl or amino;

or a salt, solvate, or physiologically functional derivative thereof.

4. A compound of formula (I) according to claim 1 selected from

(E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}-  
1-hydroxyurea;

(E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-  
1-hydroxyurea;

(E)-1-{3-[4-Cyano-3-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[2-Cyano-5-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[2-Cyano-3-phenoxyphenyl]-1-methylprop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[3-(4-Cyanophenoxy)phenyl]prop-2-enyl}-1-hydroxyurea;

(E)-1-{3-[5-(4-Cyanophenoxy)-2-cyanophenyl]-1-methylprop-2-enyl}-  
1-hydroxyurea;

(E)-1-{3-[2-Cyano-5-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-  
1-hydroxyurea;

(E)-1-{3-[2-Cyano-3-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-  
1-hydroxyurea;

(E)-1-{3-[2-Cyano-3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-  
1-hydroxyurea;

(E)-1-{3-[3-(4-Cyanophenoxy)-2-cyanophenyl]-1(R)-methylprop-2-enyl}-  
1-hydroxyurea;

(E)-1-{3-[4-Cyano-3-(4-fluorophenoxy)phenyl]-1-methylprop-2-enyl}-  
1-hydroxyurea;

(E)-1-{3-[3-(4-mesyloxyphenyl)-1-methylprop-2-enyl]-1-hydroxyurea;



(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-  
acetohydroxamic acid;

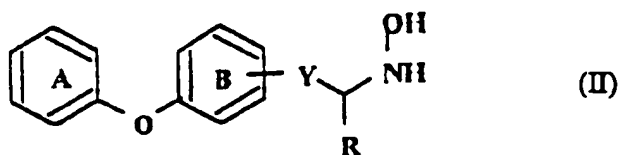
(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}-  
acetohydroxamic acid;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}acetohydroxamic  
acid;  
N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}acetohydroxamic  
acid;

or a salt, solvate, or physiologically functional derivative thereof.

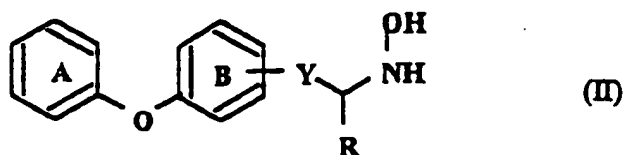
5. (E)-1-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-1-hydroxyurea or  
a salt, solvate, or physiologically functional derivative thereof.
6. (E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-  
acetohydroxamic acid or a salt, solvate, or physiologically functional derivative  
thereof.
7. A salt according to Claims 1 - 6 which is the calcium salt.
8. A method for the prophylaxis or treatment of a clinical condition in a mammal  
for which an inhibitor of the lipoxigenase or cyclooxygenase mediated  
arachadonic acid metabolic pathway is indicated which comprises  
administration of a therapeutically effective amount of a compound of formula  
(I) according to claims 1 - 7, or a pharmaceutically acceptable salt, solvate, or  
physiologically functional derivative thereof.
9. A method according to claim 8 wherein the clinical condition is asthma.
10. A compound of formula (I) according to claims 1 - 7, or a pharmaceutically  
acceptable salt, solvate, or physiologically functional derivative thereof, for use  
in medical therapy.

11. Use of a compound of formula (I), according to claims 1 - 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which an inhibitor of the lipoxigenase or cyclooxygenase mediated arachadonic acid metabolic pathway is indicated.
12. A pharmaceutical formulation comprising a compound of formula (I) according to claims 1 - 7, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
13. A process for preparing the compounds of formula (I), according to claims 1 - 7, or salts, solvates, or physiologically functional derivatives thereof which comprises reacting a compound of formula (II)



wherein Y, R, and the substituents on rings A and B are as defined for the compound of formula (I), according to claims 1 - 7, or a salt thereof, with a suitable agent or agents to effect conversion of the N-hydrogen to an N-COD group, where D is C<sub>1-4</sub> alkyl, or -NR<sup>4</sup>R<sup>5</sup> (wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from hydrogen and C<sub>1-4</sub> alkyl); followed by optional conversion to a salt, solvate, or physiologically functional derivative thereof.

14. Compounds of formula (II)



wherein Y, R, and the substituents on rings A and B are as defined for compounds of formula (I), according to claims 1 - 7, or a salt thereof.

15. A compound of formula (II), or a salt thereof, according to claim 14 selected from

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(R)-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-hydroxyammonium p-toluenesulphonate;

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-enyl}-hydroxylamine; and

(E)-N-{3-[3-(4-cyanophenoxy)phenyl]-1(S)-methylprop-2-ynyl}-hydroxylamine.

## INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/GB 93/01585

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07C259/06 C07C275/64 A61K31/17 A61K31/275

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 299 761 (WELLCOME) 18 January 1989 see claims; examples ---	1,2,8-13
Y	EP,A,0 196 184 (WELLCOME) 1 October 1986 cited in the application see claims; example 83 ---	1,2,8-14
Y	WO,A,92 10469 (PFIZER) 25 June 1992 cited in the application see claims; examples 1-7 ---	1,3,8-14
Y	WO,A,92 01682 (ABBOTT LABORATORIES) 6 February 1992 cited in the application see claims; examples 33-44,69-71 -----	1,3,8-14

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

27 October 1993

Date of mailing of the international search report

- 9. 11. 93

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/GB 93/01585

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP-A- 0540673	12-05-93

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